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Editorial

Preface: Zebrafish Models of Neurology☆

Forming hypotheses about the Molecular Basis of Neurological Disease has traditionally been based on human genetics, biochemistry and molecular biology, whereas testing these hypotheses requires us to turn to cell culture and animal models. Zebrafish have emerged as a tractable platform to complement and bridge these paradigms in many diseases, allowing integration of human genetics and cell biology within the *in vivo* setting. Perhaps it is in Neurology and Neurodegeneration, however, where zebrafish have special promise to make contributions. Four special advantages of zebrafish to Neurology are worth highlighting here: efficient in vivo tests for genetic interactions, conserved cellular architecture of the CNS, the ability to create genetically mosaic animals, and tractable behaviour and electrophysiology to assess experimental interventions.

Linkages between Neurodegenerative diseases that were once considered distinct are being recognized and celebrated as a path forward to understanding the molecular basis of disease spread through the CNS. One example includes interactions between notorious proteins in Alzheimer Disease (AD) and Prion Disease, such that the Prion Protein may now be viewed as a receptor for Aβ oligomers. The abundance of such interactions between Neurological Diseases is growing, as protein interactome studies identify many players in common, compelling the field to integrate an increasing list of genetic interactions into their models. The ability to efficiently knockdown and overexpress gene products *in vivo* is propelling zebrafish to prominence at a rate commensurate with the complexity of these genetic interactions.

On the other hand, various researchers have recently noted intriguing parallels between prion diseases and the protein misfolding in other neurological diseases. In particular, questions are being raised as to the ability of misfolded proteins (including Tau and Aβ) to induce the misfolding of normally folded protein, leading to a prion-like domino effect and accumulation of protein dysfunction/aggregation that are hallmark disease pathologies. Consistent with such findings is the apparent spreading of disease pathology from a nucleation centre through the CNS during clinical disease progression. Other celebrated potential prion-like proteins include α-synuclein, polyglutamine proteins and SOD1 misfolding in ALS.

Attention toward this prionoid nature of various neurological diseases is substantial, in large part because it identifies a novel therapeutic target: the mechanism of disease spreading. Unfortunately, the field knows remarkably little about disease spreading, with concepts in high-profile reviews centering on Tunneling Nanotubes and exosome or synaptic release. Perhaps this fundamental lack of knowledge regarding disease spread through the CNS is the consequence of the tools available to neurologists and neuroscience researchers. The mechanisms underlying AD, TSEs, and ALS have benefitted primarily from biochemistry/ biophysics of protein aggregation, cell culture work and mouse models; These paradigms are challenging to implement in a fashion that tells us how disease in one portion of the CNS spreads to another. Zebrafish are positioned brilliantly to fill this gap, not only because of its efficiency as a genetic and neuroscience model, but because zebrafish have a long history as a platform for assessing non-cell-autonomous effects of protein perturbations in the *in vivo* setting. Thus it is common for zebrafish biologists to ask if changing gene abundance or character in one group of neurons is able to affect the fate and function of neighboring cells. Creative and ambitious deployment of this ability will complement established tools to promise a deep understanding of how disease spreads between cells. A tantalizing side-benefit is the ability to deploy the fish in high-throughput screens of protein and small molecule effectors that represent therapeutic targets.

Finally, it is important to underline the cellular context of disease spreading during Neurolodegeneration. As disease spreads from cell to cell, the molecular basis of this spread is fundamentally influenced by the cellular relationships. Importantly, The zebrafish has an architecture of CNS cells that is conserved with that of humans. Vasculature, blood-brain-barriers, and ventricles are all present from a young age, permitting tissue-level spread of molecules fundamental to disease. Perhaps more importantly, the cells of the CNS develop in their normal environment, becoming polarized, interconnected and ensheathed in radial glia to form ion sinks. The cover image selected is meant to highlight that this organization exists even in young embryos. Certainly our understanding of hallmark synaptic dysfunction during Neurodegeneration must develop from paradigms where synapses are formed and maintained with their typical glial partners intact. So although zebrafish is not yet as advanced in its toolkit as *Drosophila*, nor as tractable as cell culture, it has a relevant cellular architecture and genetic efficiency that make the paradigm a very attractive *in vivo* complement to studies in mouse models.

This issue of *BBA: Molecular Basis of Disease* has invited reviews from leading experts to consider the utility of zebrafish to Neurology. These experts span from Neuroscientists who study fundamentals of zebrafish Biology, through to clinical Neurologists who recognize the zebrafish as a relevant and potent paradigm to bring their hypotheses to bedside in as timely a manner as possible. The first contributions have sought to critically analyze previous work regarding particular Neurodegenerative diseases and how zebrafish have contributed to this understanding. The subsequent contributions consider technical opportunities and challenges of using zebrafish genetics and behavioural outputs in Neurology, and the issue ends with the promise provided by zebrafish to understand regeneration of the CNS for repair.

I am grateful to each of these contributors, reviewers, and the BBA staff for their hardwork in communicating these important and stimulating ideas.

☆ This article is part of a Special Issue entitled Zebrafish Models of Neurological Diseases.

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Allison is a neuroscientist with a special interest in understanding processes of neurodegeneration and neural regeneration. Towards this goal, Dr. Allison's research integrates molecular biology, biochemistry, proteomics, and electrophysiology to further develop zebrafish as a potent animal model. Particular emphasis of his research has been developing fish as effective models of neurodegenerative disease. He completed a Doctoral Program in 2004 with Professor Craig Hawryshyn at the University of Victoria, Canada, where he developed a unique model of neuronal degeneration and regeneration. This work was funded by fellowships from the Alzheimer Society of Canada and the Canadian Institute of Health Research Institute of Aging. Dr. Allison went on to complete an NSERC Post-Doctoral fellowship at the University of Michigan in the laboratory of Collegiate Professor Pamela Raymond. Dr. Allison's work at the University of Michigan created transgenic and mutant zebrafish has revealed genes important in the generation, positioning, and regeneration of neurons. Dr. Allison joined the Centre for Prions and Protein Folding Diseases as an Assistant Professor at the University of Alberta, Canada in 2008. His appointment is through the Department of Biological Sciences in the Faculty of Science, with a cross-appointment in the Department of Medical Genetics in the Faculty of Medicine and Dentistry. Dr. Allison is contributing to expanding the largest zebrafish facility in Western Canada and also maintains active research in the field of retina development and regeneration. His current research efforts focus on creating transgenic and mutant zebrafish to address hypotheses of prion protein's normal function and to dissect the role of various prion protein domains. Other efforts use similar methods to examine the amyloid hypothesis of Alzheimer Disease. His Recent work is funded by a Recruitment Grant from PrioNet Canada and the Alberta Prion Research Institute and by a Young Investigators Award from the Alzheimer Society of Canada.

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